Unraveling the helianane family: A Complementary Quantum Mechanical Study

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Supplementary information

Calculations:

All density functional theory (DFT) calculations were carried out at 298 K in Gaussian 09 software.[46] All conformational searches were carried out at the molecular mechanics level of theory with the Monte Carlo algorithm employing the MMFF force field at SPARTAN'10 software.[47] Initially, for each molecule, all conformations within a 10 kcal mol^{-1} window were then fully optimized at the mPW1PW91/6-31G(d) level. The conformers with relative energy < 2.0 kcal mol^{-1}, which correspond to more than 90% of the total Boltzmann distribution, were selected for GIAO NMR calculations. To simulate the ^{13}C NMR chemical shift, it was performed a Gauge Included Atomic Orbitals-Hybrid Density Functional Theory (GIAO-HDFT) calculation procedure at the GIAO/mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) level of theory, where the

geometry optimizations were followed by absolute isotropic ^{13}C magnetic shielding constants calculations for the both possible structures (σ_i, i = 1 to 15) and TMS (σ_0) as internal reference at the same level of theory. The predicted ^{13}C-NMR chemical shifts ($\delta_i = \sigma_0 - \sigma_i$) were then scaled by a factor obtained from linear correlation between the calculated and experimental chemical shifts of a pool of adequately chosen compounds, as $\delta_{scal} = a \times \delta_i + b$ ($\delta exp = 1.06\delta_{calc} - 2.19$).[36]

The energy change for the conversion of curcuphenol **4** to helianane **1** and curcudiol **6** was simulated by means of DFT employing the long-range corrected functional ωB97X-D with 6-31++G(d,p) basis set function. This level of theory has shown to be suitable in the description of reactions pathway involving hydrogen bonding and proton transfers.[48] The Berny algorithm for minimizations to local minima and first-order saddle points (TS) was employed using the GEDIIS procedure. We characterized the nature of the stationary points by vibrational frequency calculation: local minimum are identified as those having only positive eigenvalues in the Hessian matrix, while any TS has just one negative eigenvalue pointing in the direction of the reaction coordinate. Polarizable Continuum Model with the Integral Equation Formalism (IEFPCM) was applied to implicitly simulate water as solvent medium

SUPPORTING TABLES AND FIGURES:

Table S1: Comparison of ^{13}C NMR data of synthetic helianane and curcudiol with the corresponding isolated natural product.

Table S2: Comparison of ^{13}C NMR data of simulated chlorinated derivatives of helianane and curcudiol with the corresponding isolated natural product.

Table S3: Comparison of ^{13}C NMR data of simulated brominated derivatives of helianane and curcudiol with the corresponding isolated natural product.

Figure S1: Comparison of the difference in ^{13}C NMR chemical shifts ($\Delta\delta$) data of synthetic helianane and curcudiol with the corresponding isolated natural product.
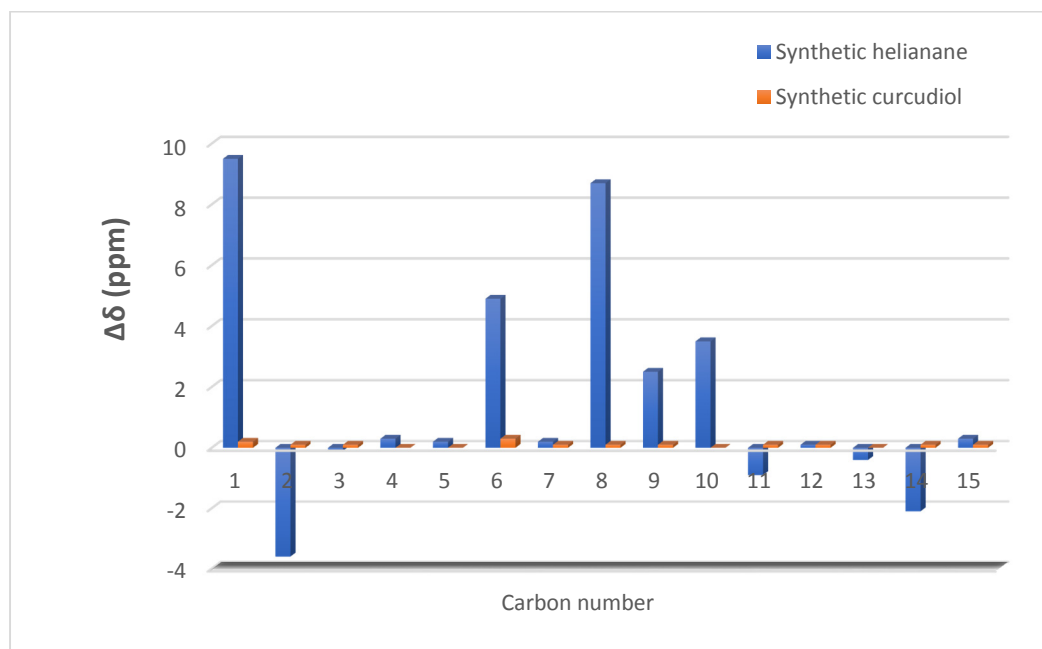
Figure S2: Comparison of the difference in ^{13}C NMR chemical shifts ($\Delta\delta$) data of simulated chlorinated derivatives of helianane and curcudiol with the corresponding isolated natural product.

Figure S3: Comparison of the difference in ^{13}C NMR chemical shifts ($\Delta\delta$) data of simulated brominated derivatives of helianane and curcudiol with the corresponding isolated natural product.
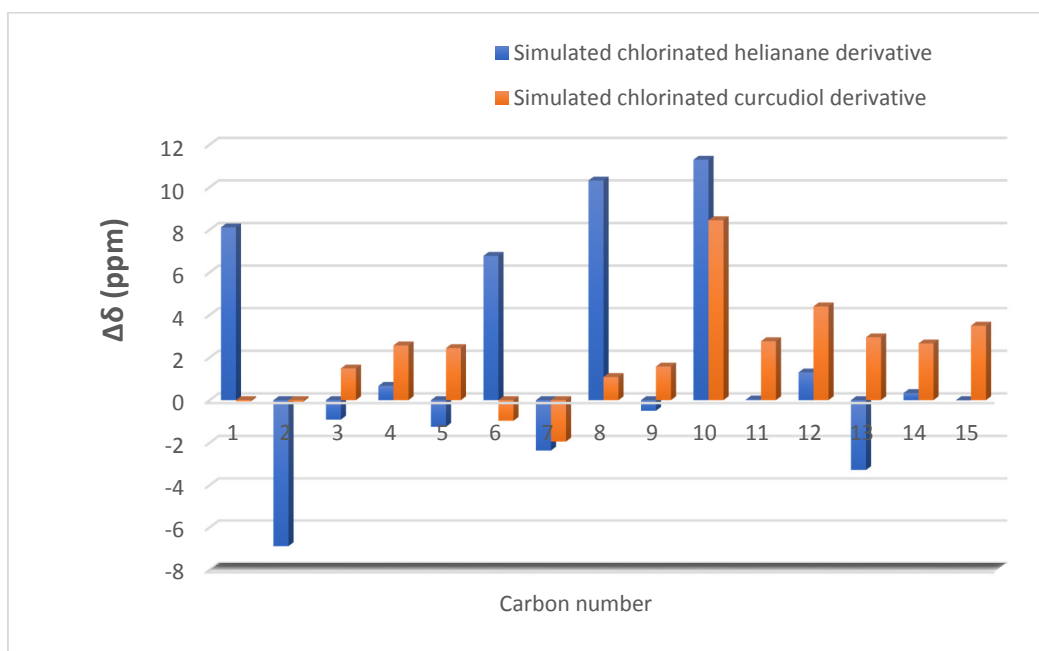
Figure S4: Structures of chlorinated derivatives of helianane and curcudiol, and C-DP4+ (scaled and unscaled forms) values calculated by correlating the calculated NMR chemical shifts of both structures with the experimental NMR data of the isolated natural product.

Figure S5: Structures of brominated derivatives of helianane and curcudiol, and C-DP4+ (scaled and unscaled forms) values calculated by correlating the calculated NMR chemical shifts of both structures with the experimental NMR data of the isolated natural product.

Figure S6: Lowest energy conformers of helianane at mPW1PW91/6-31G(d) level:

Figure S7: Lowest energy conformers of curcudiol at mPW1PW91/6-31G(d) level:

Figure S8: Lowest energy conformers of helianane chlorinated derivative at mPW1PW91/6-31G(d) level:

Figure S9: Lowest energy conformers of curcudiol chlorinated derivative at mPW1PW91/6-31G(d) level:

Figure S10: Lowest energy conformers of helianane brominated derivative at mPW1PW91/6-31G(d) level:

Figure S11: Lowest energy conformers of curcudiol brominated derivative at mPW1PW91/6-31G(d) level:

Figure S12: Structures involved on the reaction pathway concerning the chemical transformation of curcuphenol **4** in acidic conditions for the formation of helianane **1** and curcudiol **6**. Values of ΔG (green) and ΔH (blue) calculated at ωB97X-D/6-31++G(d,p) computational level.

SUPPORTING TABLES AND FIGURES:

Table S1: Comparison of ^{13}C NMR data of synthetic helianane and curcudiol with the corresponding isolated natural product.

Atom number	Synthetic helianane[b] (δ)	Synthetic curcudiol[b] (δ)	Isolated natural product[a] (δ)
C1	81.1	71.8	71.6
C2	39.8	43.5	43.4
C3	22.1	22.3	22.2
C4	38.1	37.8	37.8
C5	31.6	31.4	31.4
C6	135.5	130.9	130.6
C7	153.3	153.2	153.1
C8	125.1	116.5	116.4
C9	139	136.6	136.5
C10	125.2	121.7	121.7
C11	126	127	126.9
C12	21.1	21.1	21
C13	29.4	29.8	29.8
C14	26.8	29	28.9
C15	21.4	21.2	21.1
MAD	2.49	0.09	
RMSD	3.89	0.12	

[a] Harrison and Crews Org. Chem. 1997.

[b] Green, Jiminez-Alonso, Brown and Pettus, Org. Lett., 2011.

Table S2: Comparison of ^{13}C NMR data of simulated chlorinated derivatives of helianane and curcudiol with the corresponding isolated natural product.

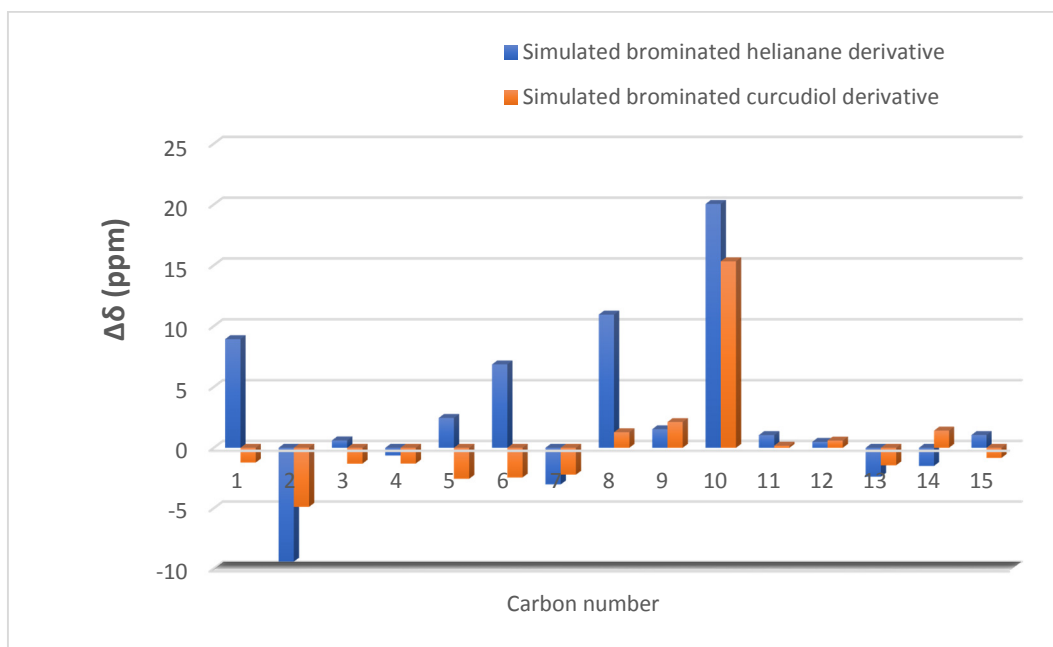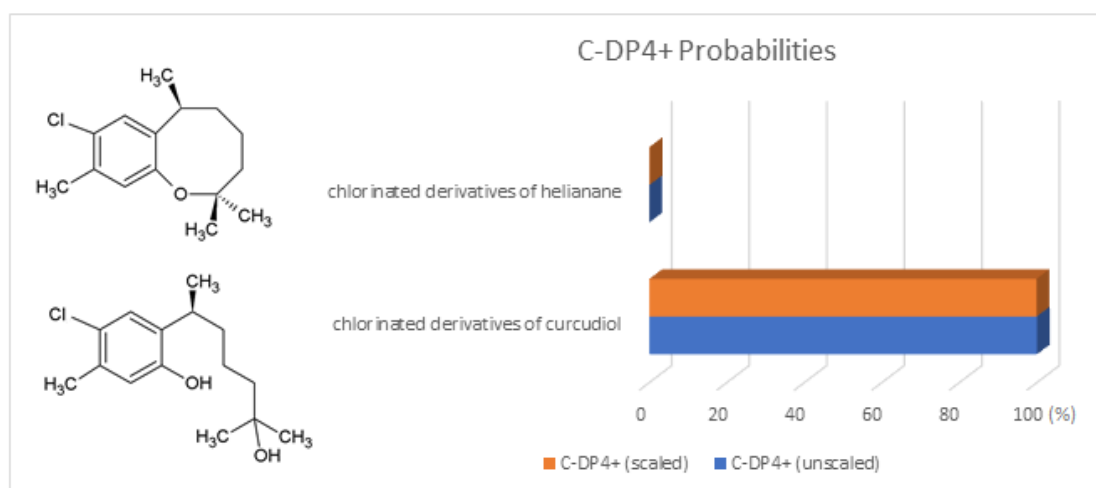| Atom number	Simulated chlorinated helianane derivative (δ)	Simulated chlorinated curcudiol derivative (δ)	Isolated natural product[a] (δ)
C1	79.61	71.45	71.5
C2	37.91	44.73	44.8
C3	22.49	24.89	23.4
C4	39.47	41.37	38.8
C5	31.75	35.45	33
C6	141.28	133.53	134.5
C7	152.33	152.75	154.7
C8	128.61	119.39	118.3
C9	133.90	135.98	134.4
C10	136.49	133.65	125.2
C11	128.13	130.87	128.1
C12	21.00	24.10	19.7
C13	25.92	32.15	29.2
C14	29.33	31.66	29
C15	21.39	24.90	21.4
MAD	**3.67**	**1.45**	
RMSD	**5.09**	**1.72**	

[a] Martín *et al.*, J. Nat. Prod. **2005**, 68, 1554-1555

Table S3: Comparison of ^{13}C NMR data of simulated brominated derivatives of helianane and curcudiol with the corresponding isolated natural product.

Atom number	Simulated chlorinated helianane derivative (δ)	Simulated chlorinated curcudiol derivative (δ)	Isolated natural product[a] (δ)
C1	80.44	70.29	71.5
C2	35.37	39.92	44.8
C3	24.01	22.10	23.4
C4	38.16	37.51	38.8
C5	35.45	30.45	33
C6	142.26	132.95	135.4
C7	152.38	153.19	155.4
C8	129.25	119.58	118.3
C9	136.43	137.02	134.9
C10	134.75	130.03	114.7
C11	132.45	131.58	131.4
C12	23.09	23.20	22.6
C13	26.92	27.87	29.3
C14	27.51	30.41	29
C15	22.45	20.57	21.4
MAD	4,73	2,61	
RMSD	7,15	4.42	

[a] Martín *et al.*, J. Nat. Prod. **2005**, 68, 1554-1555

Figure S1: Comparison of the difference in ^{13}C NMR chemical shifts ($\Delta\delta$) data of synthetic helianane and curcudiol with the corresponding isolated natural product.

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Figure S3: Comparison of the difference in ^{13}C NMR chemical shifts ($\Delta\delta$) data of simulated brominated derivatives of helianane and curcudiol with the corresponding isolated natural product.

Figure S4: Structures of chlorinated derivatives of helianane and curcudiol, and C-DP4+ (scaled and unscaled forms) values calculated by correlating the calculated NMR chemical shifts of both structures with the experimental NMR data of the isolated natural product*.

* Martín *et al.*, J. Nat. Prod. **2005**, 68, 1554-1555

Figure S5: Structures of brominated derivatives of helianane and curcudiol, and C-DP4+ (scaled and unscaled forms) values calculated by correlating the calculated NMR chemical shifts of both structures with the experimental NMR data of the isolated natural product*.
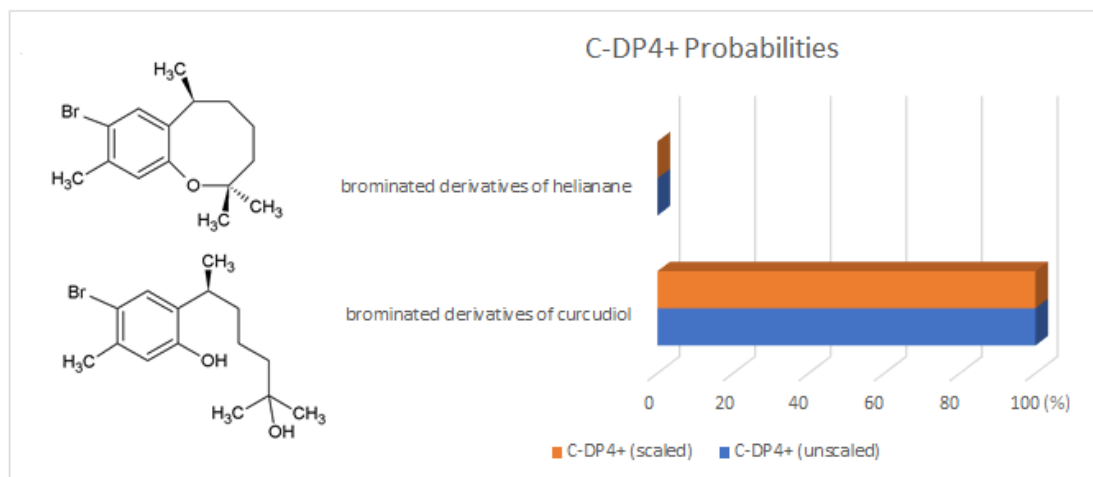
* Martín *et al.,* J. Nat. Prod. **2005**, 68, 1554-1555

Figure S6: Lowest energy conformers of helianane at mPW1PW91/6-31G(d) level:


Conf. 1, 0.0 kcal⁻¹ (56%)

Conf. 2, +0.5 kcal⁻¹ (21%)

Conf. 3, +0.6 kcal⁻¹ (21%)
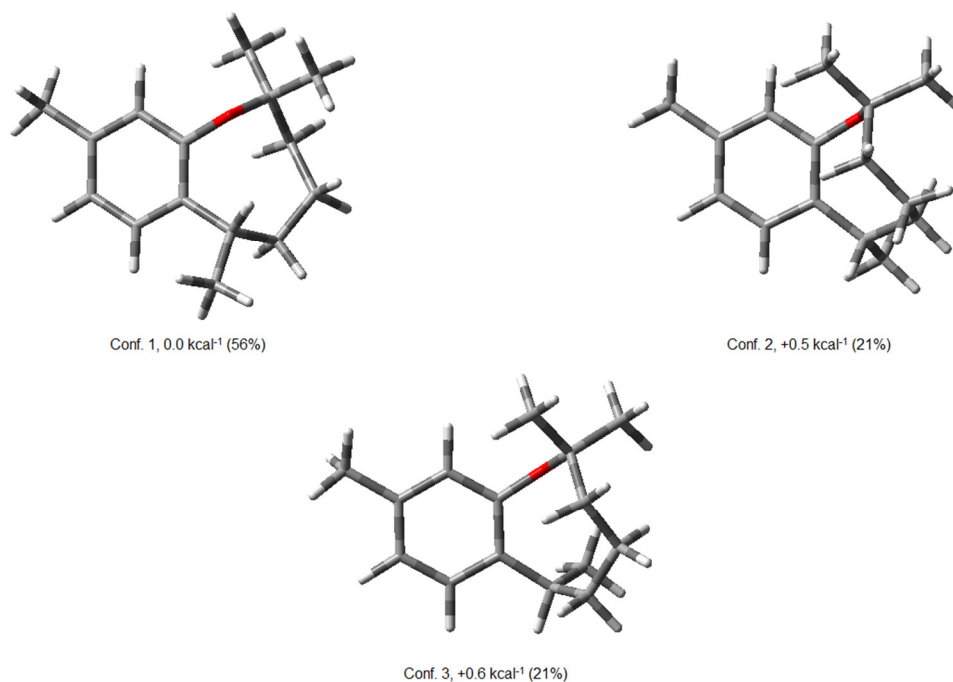
Helianane: 07 conformers with relative energy within 10 kcal mol^{-1} of the lowest energy conformer were selected for further geometry optimized at the mPW1PW91/6-31G* level. The 03 conformers were identified with relative energy <2.0 kcal mol^{-1}, corresponding to more than 99% of the total Boltzmann distribution.

Figure S7: Lowest energy conformers of curcudiol at mPW1PW91/6-31G(d) level:
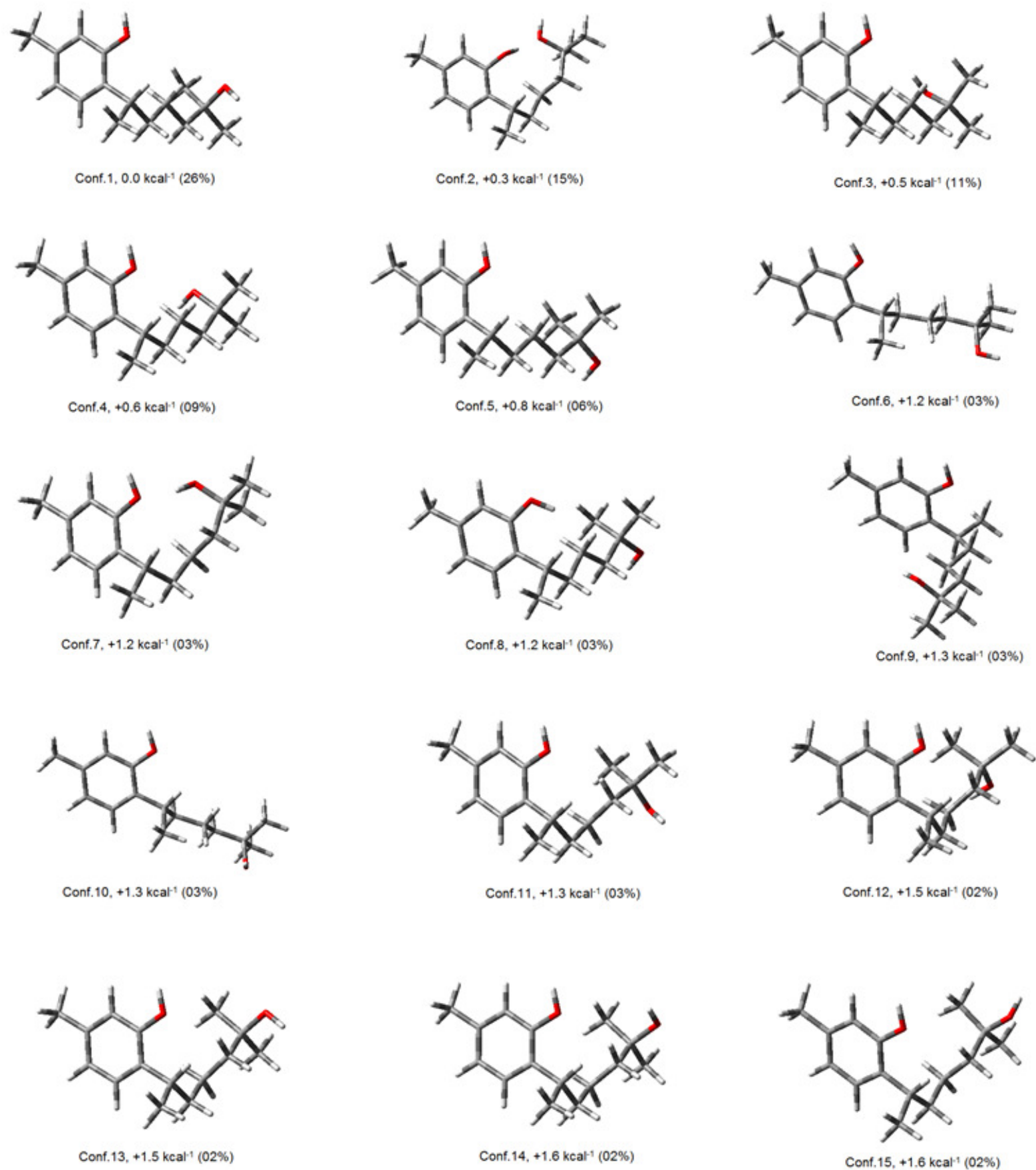
Conf.1, 0.0 kcal⁻¹ (26%)

Conf.2, +0.3 kcal⁻¹ (15%)

Conf.3, +0.5 kcal⁻¹ (11%)

Conf.4, +0.6 kcal⁻¹ (09%)

Conf.5, +0.8 kcal⁻¹ (06%)

Conf.6, +1.2 kcal⁻¹ (03%)

Conf.7, +1.2 kcal⁻¹ (03%)

Conf.8, +1.2 kcal⁻¹ (03%)

Conf.9, +1.3 kcal⁻¹ (03%)

Conf.10, +1.3 kcal⁻¹ (03%)

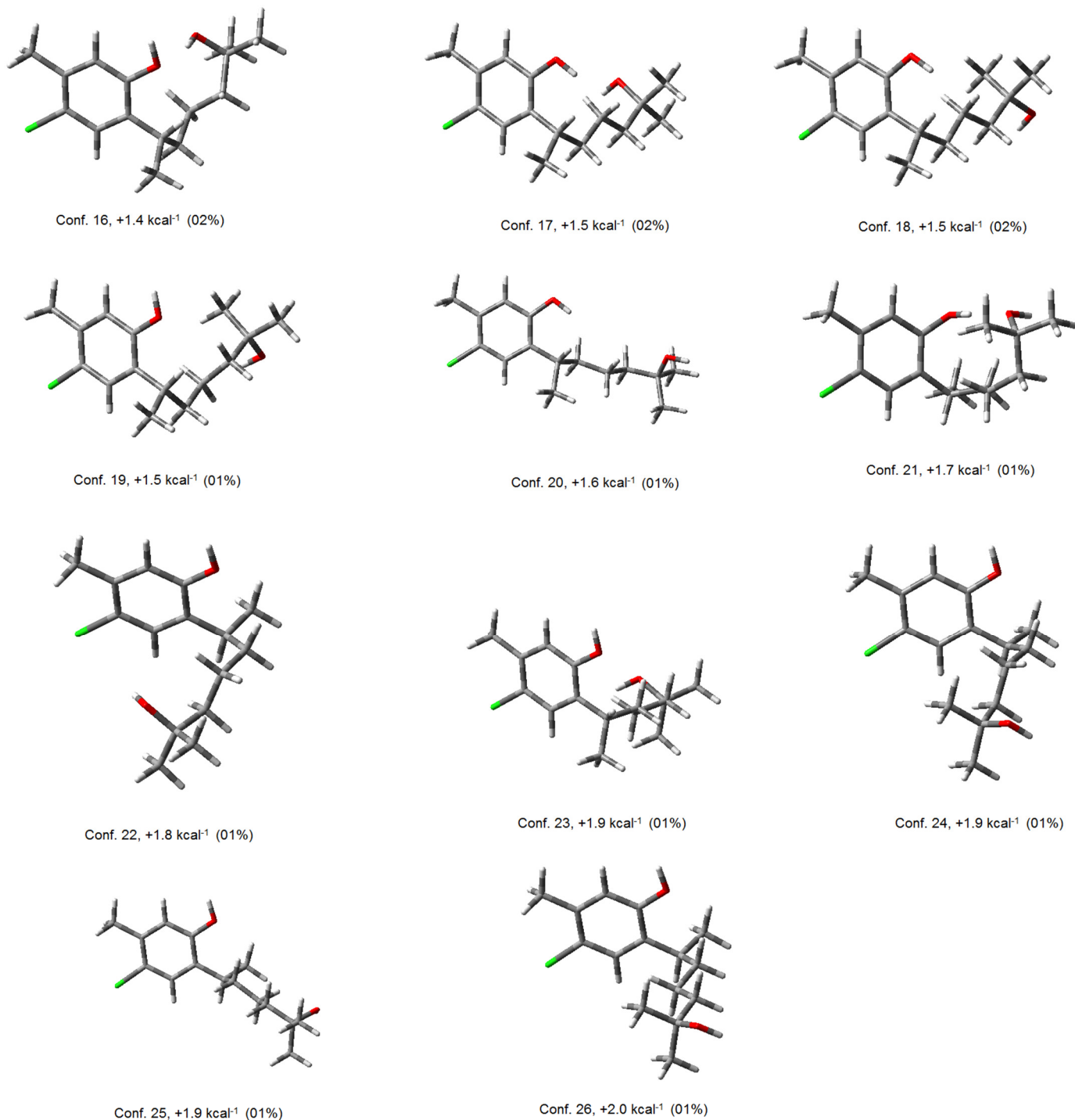Conf.11, +1.3 kcal⁻¹ (03%)

Conf.12, +1.5 kcal⁻¹ (02%)

Conf.13, +1.5 kcal⁻¹ (02%)

Conf.14, +1.6 kcal⁻¹ (02%)

Conf.15, +1.6 kcal⁻¹ (02%)

Figure S7: Lowest energy conformers of curcudiol at mPW1PW91/6-31G(d) level: Continuation:
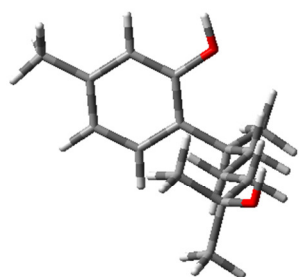
Conf.16, +1.7 kcal⁻¹ (02%)
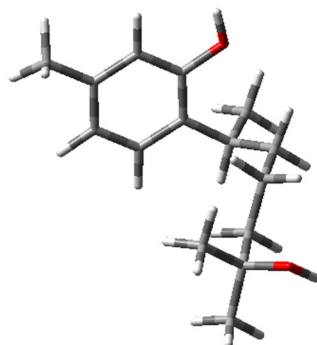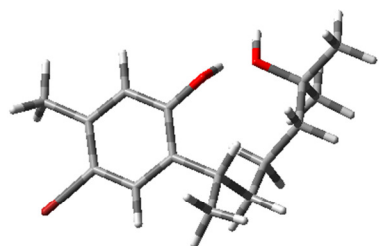
Conf.17, +1.7 kcal⁻¹ (01%)
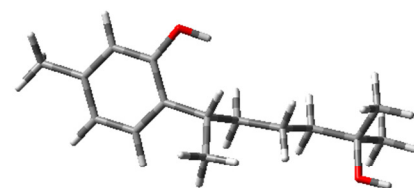
Conf.18, +1.8 kcal⁻¹ (01%)
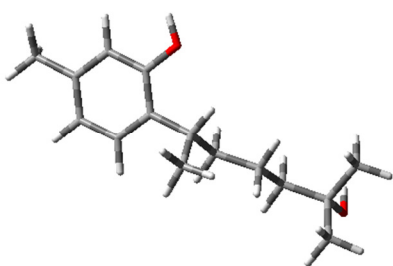
Conf.19, +1.8 kcal⁻¹ (01%)
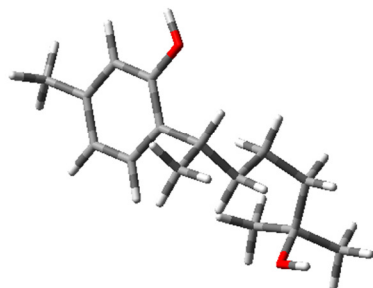
Conf. 20, +1.9 kcal⁻¹ (01%)
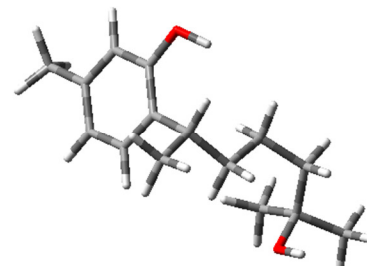
Conf. 21, +1.9 kcal⁻¹ (01%)

Curcudiol: due to it higher confomational freedom, 99 conformers with relative energy within 10 kcal mol^{-1} of the lowest energy conformer were selected for further geometry optimized at the mPW1PW91/6-31G* level. The 21 conformers were identified with relative energy <2.0 kcal mol^{-1}, corresponding to more than 90% of the total Boltzmann distribution.

**Figure S8:** Lowest energy conformers of helianane chlorinated derivative at mPW1PW91/6-31G(d) level:

Conf. 1, 0.0 kcal⁻¹ (47%)

Conf. 2, +0.02 kcal⁻¹ (46%)

Conf. 3, +1.0 kcal⁻¹ (07%)
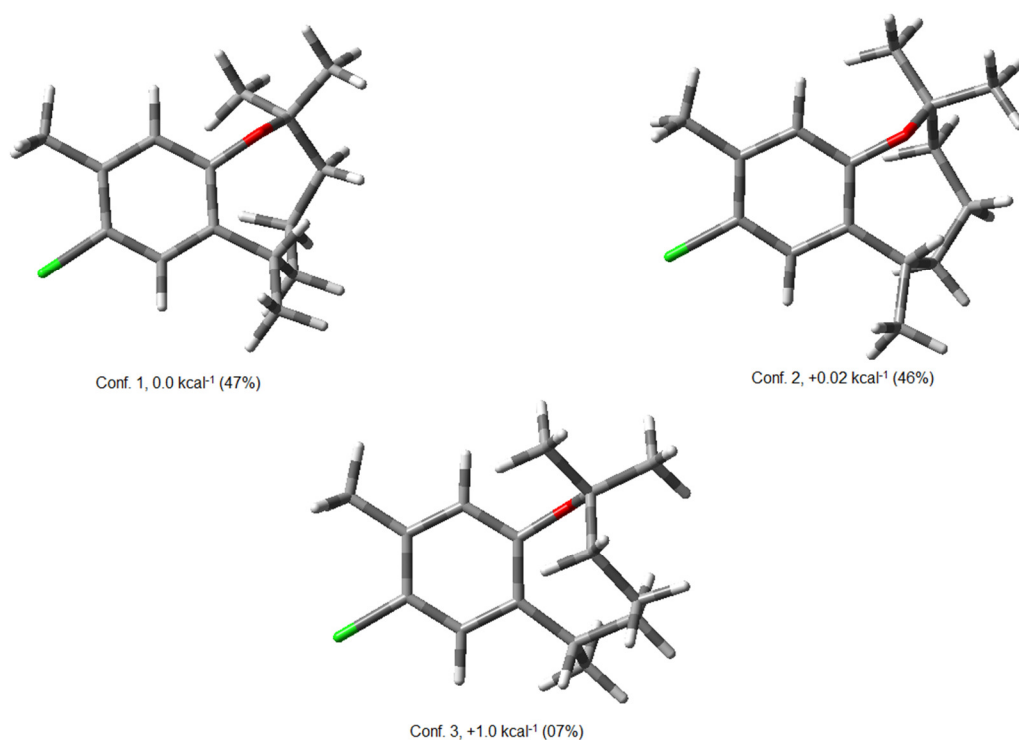
Helianane chlorinated derivative: 08 conformers with relative energy within 10 kcal mol^{-1} of the lowest energy conformer were selected for further geometry optimized at the mPW1PW91/6-31G* level. The 03 conformers were identified with relative energy <2.0 kcal mol^{-1}, corresponding to more than 99% of the total Boltzmann distribution.
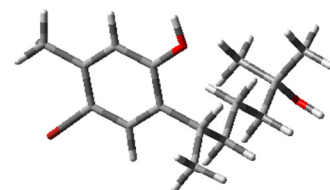
**Figure S9:** Lowest energy conformers of curcudiol chlorinated derivative at mPW1PW91/6-31G(d) level:
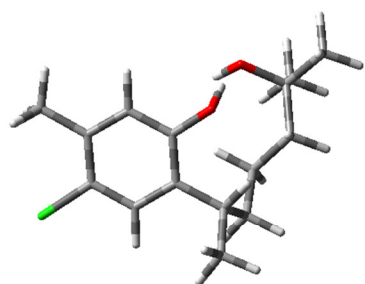

Conf. 1, 0.0 kcal^{-1} (21%)
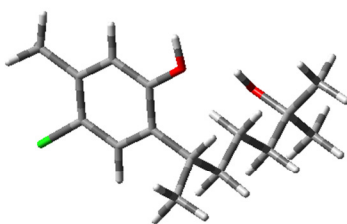
Conf. 2, +0.4 kcal^{-1} (11%)
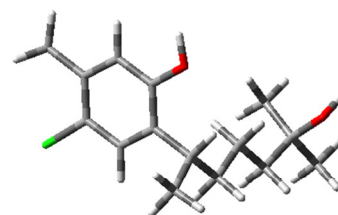
Conf. 3, +0.4 kcal^{-1} (10%)
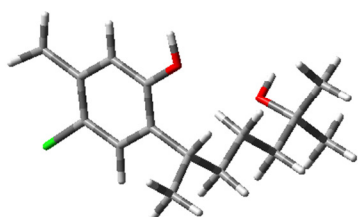
Conf. 4, +0.6 kcal^{-1} (07%)
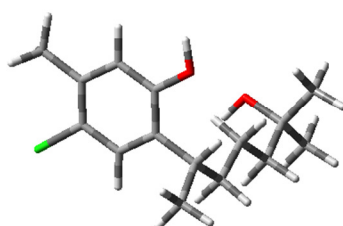
Conf. 5, +0.6 kcal^{-1} (07%)
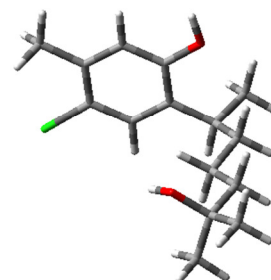
Conf. 6, +0.8 kcal^{-1} (05%)
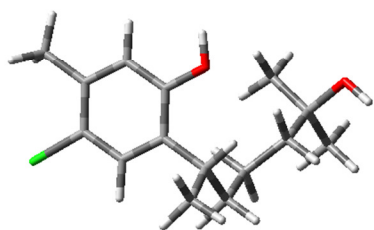
Conf. 7, +1.0 kcal^{-1} (04%)
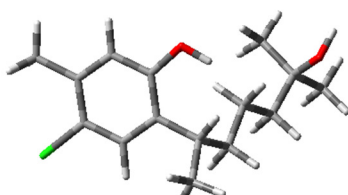
Conf. 8, +1.2 kcal^{-1} (03%)
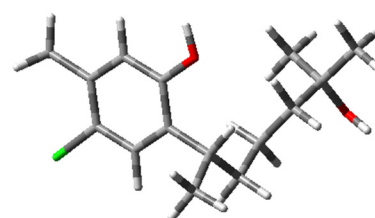
Conf. 9, +1.2 kcal^{-1} (03%)
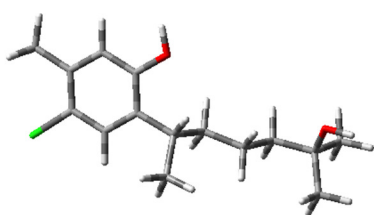
Conf. 10, +1.2 kcal^{-1} (03%)
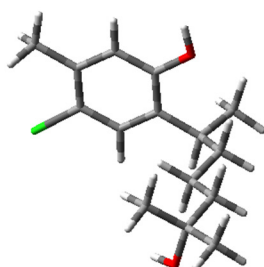
Conf. 11, +1.3 kcal^{-1} (03%)
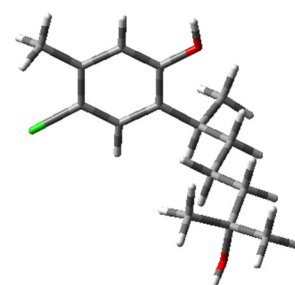
Conf. 12, +1.3 kcal^{-1} (03%)
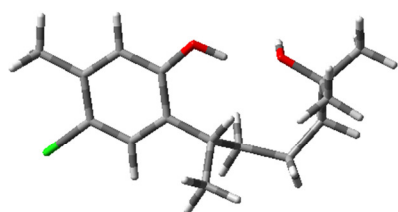
Conf. 13, +1.3 kcal^{-1} (02%)
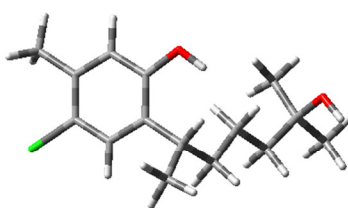
Conf. 14, +1.3 kcal^{-1} (02%)
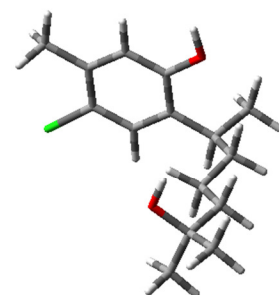
Conf. 15, +1.3 kcal^{-1} (02%)

Figure S9: Lowest energy conformers of curcudiol chlorinated derivative at mPW1PW91/6-31G(d) level: Continuation:

Conf. 16, +1.4 kcal⁻¹ (02%)

Conf. 17, +1.5 kcal⁻¹ (02%)

Conf. 18, +1.5 kcal⁻¹ (02%)

Conf. 19, +1.5 kcal⁻¹ (01%)

Conf. 20, +1.6 kcal⁻¹ (01%)

Conf. 21, +1.7 kcal⁻¹ (01%)

Conf. 22, +1.8 kcal⁻¹ (01%)

Conf. 23, +1.9 kcal⁻¹ (01%)

Conf. 24, +1.9 kcal⁻¹ (01%)

Conf. 25, +1.9 kcal⁻¹ (01%)

Conf. 26, +2.0 kcal⁻¹ (01%)

Curcudiol chlorinated derivative: due to it higher confomational freedom, 98 conformers with relative energy within 10 kcal mol^{-1} of the lowest energy conformer were selected for further geometry optimized at the mPW1PW91/6-31G* level. The 26 conformers ware identified with relative energy <2.0 kcal mol^{-1}, corresponding to more than 92% of the total Boltzmann distribution.

Figure S10: Lowest energy conformers of helianane brominated derivative at mPW1PW91/6-31G(d) level:

Conf. 1, 0.0 kcal⁻¹ (68%)

Conf. 2, +0.7 kcal⁻¹ (19%)

Conf. 3, +1.0 kcal⁻¹ (13%)
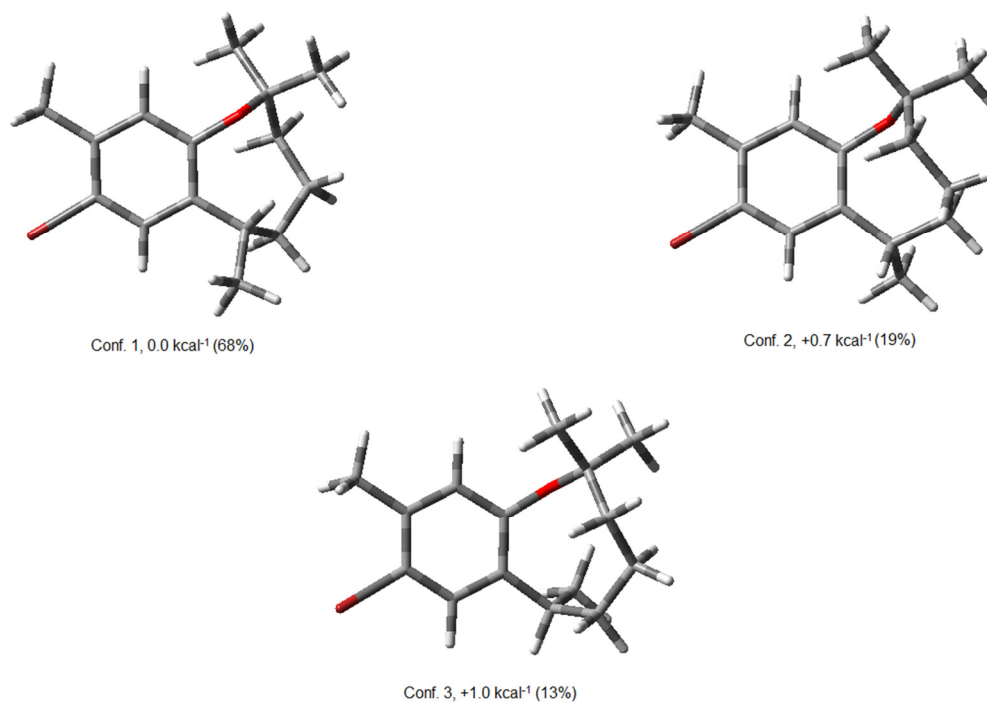
Helianane brominated derivative: 07 conformers with relative energy within 10 kcal mol^{-1} of the lowest energy conformer were selected for further geometry optimized at the mPW1PW91/6-31G* level. The 03 conformers were identified with relative energy <2.0 kcal mol^{-1}, corresponding to more than 98% of the total Boltzmann distribution.

Figure S11: Lowest energy conformers of curcudiol brominated derivative at mPW1PW91/6-31G(d) level:

Conf.1, 0.0 kcal^{-1} (30%)
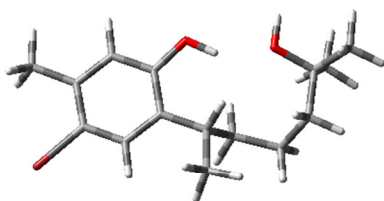
Conf.2, +0.2 kcal^{-1} (24%)

Conf.3, +0.6 kcal^{-1} (11%)
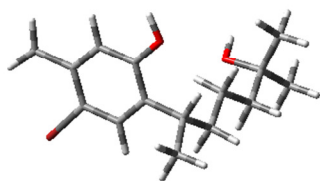
Conf.4, +0.8 kcal^{-1} (08%)
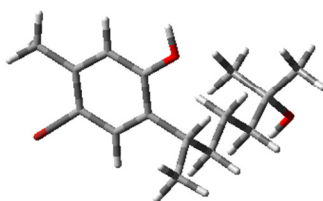
Conf.5, +0.9 kcal^{-1} (07%)
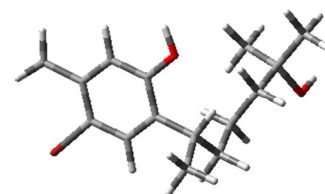
Conf.6, +1.7 kcal^{-1} (02%)
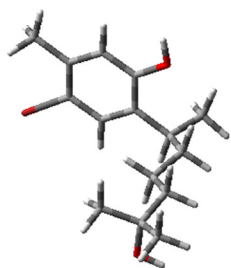
Conf.7, +1.7 kcal^{-1} (02%)
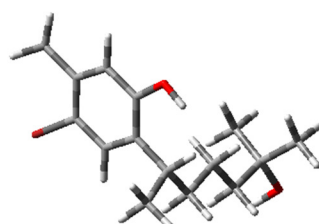
Conf.8, +1.7 kcal^{-1} (02%)
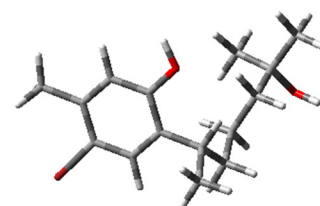
Conf.9, +1.8 kcal^{-1} (02%)
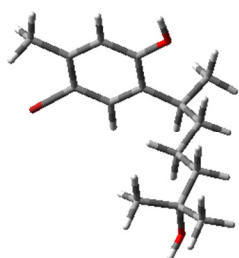
Conf.10, +1.8 kcal^{-1} (01%)
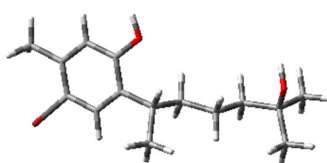
Conf.11, +1.9 kcal^{-1} (01%)
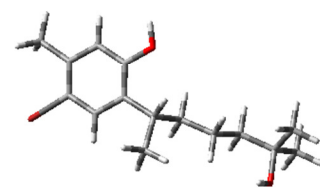
Conf.12, +1.9 kcal^{-1} (01%)
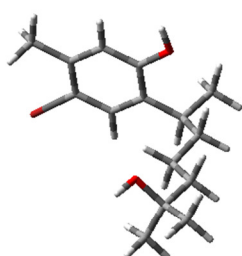
Conf.13, +1.9 kcal^{-1} (01%)
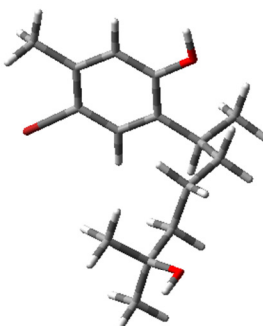
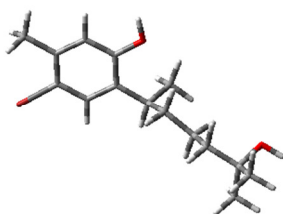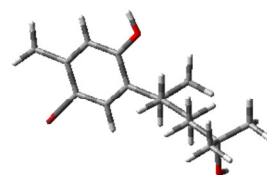Conf.14, +2.0 kcal^{-1} (01%)
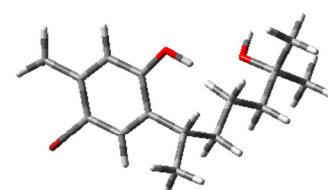
Conf.15, +2.0 kcal^{-1} (01%)

Figure S11: Lowest energy conformers of curcudiol brominated derivative at mPW1PW91/6-31G(d) level: Continuação:
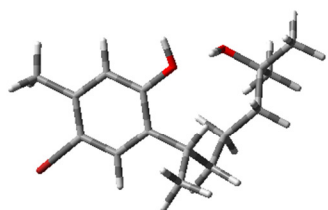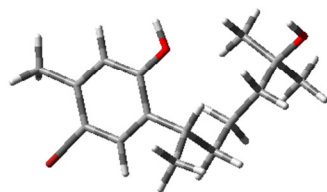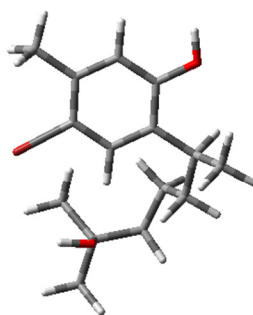

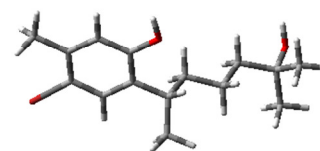Conf.16, +2.1 kcal⁻¹ (01%)

Conf.17, +2.2 kcal⁻¹ (0.8%)

Conf.18, +2.2 kcal⁻¹ (0.7%)
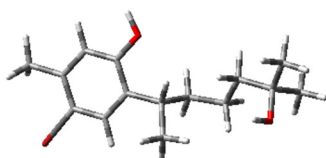
Conf.19, +2.3 kcal⁻¹ (0.6%)
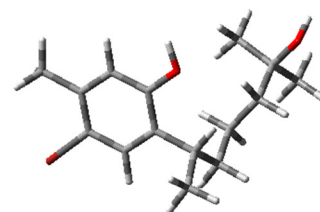
Conf. 20, +2.3 kcal⁻¹ (0.6%)

Conf. 21, +2.4 kcal⁻¹ (0.6%)

Conf. 22, +2.4 kcal⁻¹ (0.6%)

Conf. 23, +2.4 kcal⁻¹ (0.6%)

Conf. 24, +2.4 kcal⁻¹ (0.5%)

Curcudiol brominated derivative: the same higher confomational freedom was obtained, were 99 conformers with relative energy within 10 kcal mol⁻¹ of the lowest energy conformer were selected for further geometry optimized at the mPW1PW91/6-31G* level. The 24 conformers were identified with relative energy <2.5 kcal mol⁻¹, corresponding to more than 93% of the total Boltzmann distribution.

Figure S12: Structures involved on the reaction pathway concerning the chemical transformation of curcuphenol **4** in acidic conditions for the formation of helianane **1** and curcudiol **6**. Values of ΔG (green) and ΔH (blue) calculated at ωB97X-D/6-31++G(d,p) computational level in kcal mol^{-1}.